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EXAMINER

HOLLERAN, ANNE L

ART UNIT	PAPER NUMBER
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1642

DATE MAILED: 01/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/635,974

Applicant(s)

TEUFEL, THOMAS

Examiner

Anne Holleran

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 26 August 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,3-5 and 45-48 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 3-5 and 45-48 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: PDR entry for CAMPTOSAR.

DETAILED ACTION

1. The amendment filed 5/20/2004 and the response to the Sequence Rules Letter filed 8/26/2004 are acknowledged. This application is now in compliance with the sequence rules. Claims 45-48 were added. Claims 1, 3-5 and 45-48 are pending and examined on the merits.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections Withdrawn:

3. The rejection of claims 1, 3 and 5 under 35 U.S.C. 103(a) as being unpatentable over Wels (U.S. Patent 6,129,915; issued 10/2000; effective filing 02/1997) or Mendelsohn (U.S. Patent 4,943,533; issued 07/1990; effective filing 03/1984; cited in IDS) in view of Varani (Varani, J. et al., Pathobiology, 66: 253-259, 1998; cited in previous Office action) and further in view of McMahon (U.S. Patent 6,004,967; issued 12/1999; effective filing 06/1997; cited in IDS) is withdrawn upon further consideration.
4. The rejection of claims 1, 3 and 4 under 35 U.S.C. 103(a) as being unpatentable over Wels (U.S. Patent 6,129,915; issued 10/2000; effective filing 02/1997) or Mendelsohn (U.S. Patent 4,943,533; issued 07/1990; effective filing 03/1984; cited in IDS) in view of Varani (Varani, J. et al., Pathobiology, 66: 253-259, 1998; cited in previous Office action) and further

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in view of Goldstein (WO 96/40210; published 12/1996; cited in a previous Office action) is withdrawn upon further consideration.

New Grounds of Rejection:

5. Claims 1, 3-5 and 45-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claimed inventions are drawn to methods of treating a mammal with psoriasis, comprising systemically administering to a mammal an amount of an EGFR/HER1 antibody effective to treat psoriasis. The mammal may be human (claim 45) and the route of systemic administration may be intravenous (claim 46). The antibody may be a monoclonal antibody or fragment that comprises the hypervariable region of the monoclonal antibody. The monoclonal antibody may be one that inhibits EGFR/HER1 phosphorylation, and also may be one that has CDRs encompassed by SEQ ID NO: 2, SEQ ID NO: 4, SEQ ID NO: 6, SEQ ID NO: 8, SEQ ID NO: 10 and SEQ ID NO: 12. These CDR sequences are the CDR sequences of the murine monoclonal antibody 225, which is an antibody known in the art (US 4,943,533; deposited). The antibody may also be C225, which is a specific chimeric version of the murine monoclonal antibody 225, having the murine variable region of the monoclonal antibody and a human constant region.

Factors to be considered in determining whether undue experimentation would be required to practice the full scope of the claimed inventions are: 1) quantity of experimentation

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necessary; 2) the amount of direction or guidance presented in the specification; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. See *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

Undue experimentation would be required to practice the full scope of the claimed inventions because the examples provided in the specification do not exemplify the full scope of the claimed inventions, and furthermore, the description of the working example is unclear so that one of skill in the art cannot determine what experiment was performed. The specification confines its teachings to methods comprising the administration to a cancer patient, who happened to also suffer from psoriasis, of a specific chimeric version of the murine 225 antibody anti-EGFR antibody in combination with a chemotherapeutic agent which is designated as "CPT-11 (cisplatin)". However, CPT-11 is not the same as cisplatin. CPT-11, also known as irinotecan hydrochloride (an alkaloid extract from plants; see PDR entry for CAMPTOSAR, irinotecan hydrochloride) is a different chemical compound from cisplatin, which has the chemical name of cis-diamminedichloro-platinum II, and is a platinum salt (see Troy, *Psycho-Oncology*, 9: 29-39, 2000, page 29). Because the specification teaches that a human cancer patient was administered a combination of the antibody C225 and a chemotherapeutic agent that was either CPT-11 or cisplatin, it is not clear whether the psoriasis was improved because of the C225 administration, the chemotherapeutic agent (CPT-11 or cisplatin) administration, or the combination of the two. In contrast to the working examples provided by the specification, the scope of the claims is broadly drawn to methods of treatment of any mammal, comprising administering an amount of any anti-EGFR/HER1 antibody.

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Varani (cited in a previous Office action) teaches that an impediment to understanding the pathophysiology of psoriasis is the lack of good experimental models (see page 254, 1st column) and that there are no animal models of psoriasis. Therefore, it is not clear that the results provided in the specification may be applicable to any mammal other than humans. Furthermore, the C225 antibody was administered in combination with a second drug, making it unclear whether the results provided in the specification may be applicable to the treatment of psoriasis comprising administration of an EGFR/HER1 antibody in an amount effective to treat psoriasis, because the specification fails to teach an amount of an EGFR/HER1 antibody effective to treat psoriasis. In view of the unclear teachings of the specification concerning the identity of the second drug combined with the C225 antibody, the lack of controls demonstrating that the C225 antibody would be effective if used alone for the treatment of psoriasis, the lack of animal models, and the lack of teachings demonstrating how results demonstrating that C225 in combination with a second drug, the identity of which is unclear, would extrapolate to the broad scope of methods comprising the use of any anti-EGFR/HER1 antibody, the practice of the claimed inventions would require further and undue experimentation on the part of the skilled worker. Therefore, the claimed inventions are not supported by the specification.

6. Claim 48 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not set forth in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 48 is drawn, in part, to a method using the C225 chimeric antibody. While the monoclonal antibody, 225, is publically available, the specification fails to describe how to make

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the specific species of chimerized 225 antibody, C225, that is referred to in claim 48.

Furthermore, the specification fails to provide enough information for one of skill in the art to produce a chimeric antibody with exactly the same characteristics as the C225 chimeric antibody, because the specification fails to provide the structure the specific C225 antibody.

Because it does not appear that the C225 chimeric antibody is publicly available, and because the specification does not provide the structure of the C225 chimeric antibody, one of ordinary skill in the art cannot be assured of the ability to practice the claimed invention that requires the use of the specific species of chimerized 225 antibody, C225. Because claim 48 specifically requires the use of the C225 chimeric antibody, a suitable deposit of the cell line producing the C225 chimeric antibody is required, or evidence must be provided that the C225 chimeric antibody is well known and readily available to the public, or that it is reproducible without undue experimentation.

Furthermore, unless a deposit was made at or before the time of filing, a declaration filed under the 37 C.F.R. 1.132 is necessary to construct a chain of custody. The declaration, executed by a person in a position to know, should identify the deposited cell line by its depository accession number, establish that the deposited cell line is the same as that described in the specification, and establish that the deposited cell line was in applicant's possession at the time of filing. Applicant is required to amend the specification to recite the accession number of the deposit, the date of deposit, a description of the deposited biological material, and the name and address of the depository. See *In re Lundak*, 773 F.2d. 1216, 227 USPQ 90 (CAFC 1985) and 37 CFR 1.801-1.809 for further information concerning deposit practice.

If the deposit is made under the provision of the Budapest Treaty, filing of an affidavit or declaration by applicant or assignees or a statement by an attorney of record who has authority and control over the conditions of deposit over his or her signature and registration number stating that the deposits have been accepted by an International Depository Authority under the provisions of the Budapest Treaty, that all restrictions upon public access to the deposit will be irrevocably removed upon the grant of a patent on this application and that the deposit will be replaced if viable samples cannot be dispensed by the depository is required. This requirement is necessary when deposits are made under the Budapest Treaty as the treaty leaves this specific matter to the discretion of each member state.

If the deposits are not made under the provisions of the Budapest Treaty, then in order to certify that the deposits comply with the criteria set forth in 37 CFR 1.801-1.809 regarding availability of deposits, assurance of compliance is required. Such assurance may be in the form of an affidavit or declaration by applicants or assignees or in the form of a statement by an attorney of record who has the authority and control over the conditions of deposit, over his or her signature and registration number, averring:

(a) that all restrictions on the availability to the public of the material will be irrevocably removed upon the granting of a patent.

(b) that the material has been deposited under conditions that ensure that access to the material will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 35 CFR 1.14 and 35 USC 122.

(c) that the deposited material will be stored with all care necessary to keep it viable and uncontaminated for a period of at least five years after the most recent request for the furnishing

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of a sample of the deposited microorganism, and in any case at least thirty (30) years after the date of a deposit or for the enforceable life of the patent, whichever is longer.

(d) that the duty to replace the deposit should the depository be unable to furnish a sample when requested due to the condition of the deposit.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Office should be directed to Anne Holleran, Ph.D. whose telephone number is (571) 272-0833. Examiner Holleran can normally be reached Monday through Friday, 9:30 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist at telephone number (703) 571-1600.

Anne L. Holleran
Patent Examiner
December 23, 2004


SHEELA HUFF
PRIMARY EXAMINER

PDR® entry for

CAMPTOSAR® (Pharmacia & Upjohn)
irinotecan hydrochloride injection
For Intravenous Use Only

WARNINGS

CAMPTOSAR Injection should be administered only under the supervision of a physician who is experienced in the use of cancer chemotherapeutic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Both forms of diarrhea may be severe. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) may be accompanied by cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by atropine (see PRECAUTIONS, General). Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide. Patients with diarrhea should be carefully monitored and given fluid and electrolyte replacement if they become dehydrated or antibiotic therapy if they develop ileus, fever, or severe neutropenia (see WARNINGS). Administration of CAMPTOSAR should be interrupted and subsequent doses reduced if severe diarrhea occurs (see DOSAGE AND ADMINISTRATION).

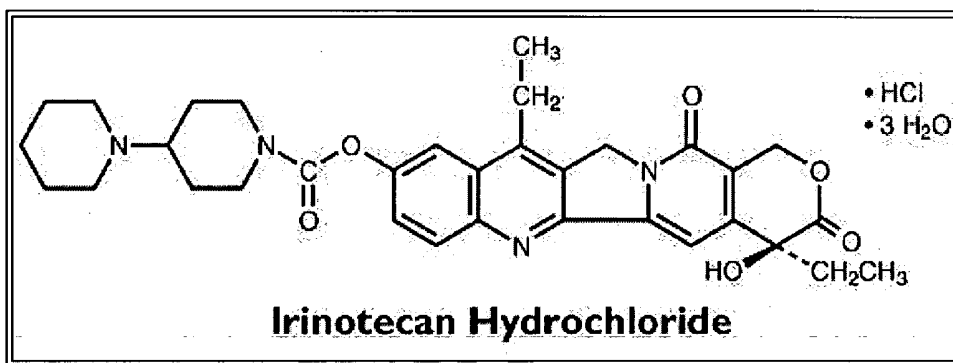
Severe myelosuppression may occur (see WARNINGS).

DESCRIPTION

CAMPTOSAR Injection (irinotecan hydrochloride injection) is an antineoplastic agent of the topoisomerase I inhibitor class. Irinotecan hydrochloride was clinically investigated as CPT-11.

CAMPTOSAR is supplied as a sterile, pale yellow, clear, aqueous solution. It is available in two single-dose sizes: 2 mL-fill vials contain 40 mg irinotecan hydrochloride and 5 mL-fill vials contain 100 mg irinotecan hydrochloride. Each milliliter of solution contains 20 mg of irinotecan hydrochloride (on the basis of the trihydrate salt), 10 mg of sorbitol NF powder, and 0.9 mg of lactic acid, USP. The pH of the solution has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. CAMPTOSAR is intended for dilution with 5% Dextrose Injection, USP (D5W), or 0.9% Sodium Chloride Injection, USP, prior to intravenous infusion. The preferred diluent is 5% Dextrose Injection, USP.

Irinotecan hydrochloride is a semisynthetic derivative of camptothecin, an alkaloid extract from plants such as *Camptotheca acuminata*. The chemical name is 4,11-diethyl-3,4,12,14-tetrahydro-4-hydroxy-3,14-dioxo-1*H*-pyrano[3',4':6,7]-indolizino[1,2-b]quinolin-9-yl-[1,4'-bipiperidine]-1'-carboxylate, monohydrochloride trihydrate. Its structural formula is as follows:



Irinotecan hydrochloride is a pale yellow to yellow crystalline powder, with the empirical formula $C_{33}H_{38}N_4O_6 \cdot HCl \cdot 3H_2O$ and a molecular weight of 677.11. It is slightly soluble in water and organic solvents.

CLINICAL PHARMACOLOGY

Irinotecan is a derivative of camptothecin. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Mammalian cells cannot efficiently repair these double-strand breaks.

Irinotecan serves as a water-soluble precursor of the lipophilic metabolite SN-38. SN-38 is formed from irinotecan by carboxylesterase-mediated cleavage of the carbamate bond between the camptothecin moiety and the dipiperidino side chain. SN-38 is approximately 1000 times as potent as irinotecan as an inhibitor of topoisomerase I purified from human and rodent tumor cell lines. In vitro cytotoxicity assays show that the potency of SN-38 relative to irinotecan varies from 2-2000-fold. However, the plasma area under the concentration versus time curve (AUC) values for SN-38 are 2% to 8% of irinotecan and SN-38 is 95% bound to plasma proteins compared to approximately 50% bound to plasma proteins for irinotecan (see Pharmacokinetics). The precise contribution of SN-38 to the anti-tumor activity of CAMPTOSAR is thus unknown. Both irinotecan and SN-38 exist in an active lactone form and an inactive hydroxy acid anion form. A pH-dependent equilibrium between the two forms such that an acid pH promotes the formation of the lactone, while a more basic pH favors the hydroxy acid anion form.

Administration of irinotecan has resulted in antitumor activity in mice bearing cancers of rodent origin and in human carcinoma xenografts of various histologies.

Pharmacokinetics

After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. The half-lives of the lactone (active) forms of irinotecan and SN-38 are similar to those of total irinotecan and SN-38, as the lactone and hydroxy acid forms are in equilibrium.

Over the recommended dose range of 50 to 350 mg/m², the AUC of irinotecan increases linearly with dose; the AUC of SN-38 increases less than proportionally with dose. Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following the end of a 90-minute infusion of irinotecan. Pharmacokinetic parameters for irinotecan and SN-38 following a 90-minute infusion of irinotecan at dose levels of 125 and 340 mg/m² determined in two clinical studies in patients with solid tumors are summarized in Table 1:

**Table 1. Summary of Mean (± Standard Deviation)
Irinotecan and SN-38 Pharmacokinetic
Parameters in Patients with Solid Tumors**

Dose (mg/m ²)	Irinotecan					SN-38		
	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)	V _z (L/m ²)	CL (L/h/m ²)	C _{max} (ng/mL)	AUC ₀₋₂₄ (ng·h/mL)	t _{1/2} (h)
125 (N=64)	1,660 ±797	10,200 ±3,270	5.8 ^a ±0.7	110 ±48.5	13.3 ±6.01	26.3 ±11.9	229 ±108	10.4 ^a ±3.1
340 (N=6)	3,392 ±874	20,604 ±6,027	11.7 ^b ±1.0	234 ±69.6	13.9 ±4.0	56.0 ±28.2	474 ±245	21.0 ^b ±4.3
C _{max} - Maximum plasma concentration								
AUC ₀₋₂₄ - Area under the plasma concentration-time curve from time 0 to 24 hours after the end of the 90-minute infusion								
t _{1/2} - Terminal elimination half-life								
V _z - Volume of distribution of terminal elimination phase								
CL - Total systemic clearance								
^a Plasma specimens collected for 24 hours following the end of the 90-minute infusion.								
^b Plasma specimens collected for 48 hours following the end of the 90-minute infusion. Because of the longer collection period, these values provide a more accurate reflection of the terminal elimination half-lives of irinotecan and SN-38.								

Irinotecan exhibits moderate plasma protein binding (30% to 68% bound). SN-38 is highly bound to human plasma proteins (approximately 95% bound). The protein to which irinotecan and SN-38 predominantly binds is albumin.

Metabolism and Excretion: The metabolic conversion of irinotecan to the active metabolite SN-38 is mediated by carboxylesterase enzymes and primarily occurs in the liver. SN-38 subsequently undergoes conjugation to form a glucuronide metabolite. SN-38 glucuronide had 1/50 to 1/100 the activity of SN-38 in cytotoxicity assays using two cell lines in vitro. The disposition of irinotecan has not been fully elucidated in humans. The urinary excretion of irinotecan is 11% to 20%; SN-38 is <1%; and SN-38 glucuronide, 3%. The cumulative biliary and urinary excretion of irinotecan and its metabolites (SN-38 and SN-38 glucuronide) over a period of 48 hours following administration of irinotecan in two patients ranged from approximately 25% (100 mg/m²) to 50% (300 mg/m²).

Pharmacokinetics in Special Populations

Geriatric: In studies using the weekly schedule, the terminal half-life of irinotecan was 6.0 hours in patients who were 65 years or older and 5.5 hours in patients younger than 65 years. Dose-normalized AUC₀₋₂₄ for SN-38 in patients who were at least 65 years of age was 11% higher than in patients younger than 65 years. A 10% increase in the starting dose is recommended for geriatric patients receiving the weekly dosage schedule of irinotecan. The pharmacokinetics of irinotecan given every 3 weeks has not been studied in the geriatric population; a lower starting dose is recommended in patients 70 years or older based on clinical toxicity experienced with this schedule (see DOSAGE AND ADMINISTRATION).

Pediatric: Information regarding the pharmacokinetics of irinotecan is not available.

Gender: The pharmacokinetics of irinotecan do not appear to be influenced by gender.

Race: The influence of race on the pharmacokinetics of irinotecan has not been evaluated.

Hepatic Insufficiency: The influence of hepatic insufficiency on the pharmacokinetic characteristics of irinotecan and its metabolites has not been formally studied. Among patients with known hepatic tumor involvement (a majority of patients), irinotecan and SN-38 AUC values were somewhat higher than values for patients without liver metastases (see PRECAUTIONS).

Renal Insufficiency: The influence of renal insufficiency on the pharmacokinetics of irinotecan has not been evaluated.

Drug-Drug Interactions

In a phase 1 clinical study involving irinotecan, 5-fluorouracil (5-FU), and leucovorin (LV) in 26 patients with solid tumors, the disposition of irinotecan was not substantially altered when the drugs were co-administered. Although the C_{max} and AUC_{0-24} of SN-38, the active metabolite, were reduced (by 14% and 8%, respectively) when irinotecan was followed by 5-FU and LV administration compared with when irinotecan was given alone, this sequence of administration was in the combination trials and is recommended (see DOSAGE AND ADMINISTRATION). Formal in vivo or in vitro drug interaction studies to evaluate the influence of irinotecan on the disposition of 5-FU and LV have not been conducted.

Possible pharmacokinetic interactions of CAMPTOSAR with other concomitantly administered medications have not been formally investigated.

CLINICAL STUDIES

Irinotecan has been studied in clinical trials in combination with 5-fluorouracil (5-FU) and leucovorin (LV) and as a single agent (see DOSAGE AND ADMINISTRATION). When given as a component of combination-agent treatment, irinotecan was either given with a weekly schedule of bolus 5-FU/LV or with every-2-week schedule of infusional 5-FU/LV. Weekly and a once-every-3-week dosage schedules were used for the single-agent irinotecan studies. Clinical combination and single-agent use are described below.

First-Line Therapy in Combination with 5-FU/LV for the Treatment of Metastatic Colorectal Cancer

Two phase 3, randomized, controlled, multinational clinical trials support the use of CAMPTOSAR Injection as first-line treatment of patients with metastatic cancer of the colon or rectum. In each study, combinations of irinotecan with 5-FU and LV were compared with 5-FU and LV alone. Study 1 compared combination irinotecan/bolus 5-FU/LV therapy given weekly with a standard bolus regimen of 5-FU/LV alone given daily for 5 days every 4 weeks; an irinotecan-alone treatment given on a weekly schedule was also included. Study 2 evaluated two different methods of administering infusional 5-FU/LV, with or without irinotecan. In both studies, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. In Study 2, a 7-day course of fluoroquinolone antibiotic prophylaxis was given in patients whose diarrhea persisted for greater than 24 hours despite loperamide. In both studies, treatment with oral fluoroquinolone was also initiated in patients who developed an absolute neutrophil count (ANC) $<500/mm^3$, even in the absence of fever or diarrhea. Patients in both studies also received treatment with intravenous antibiotics if they had persistent diarrhea or if ileus developed.

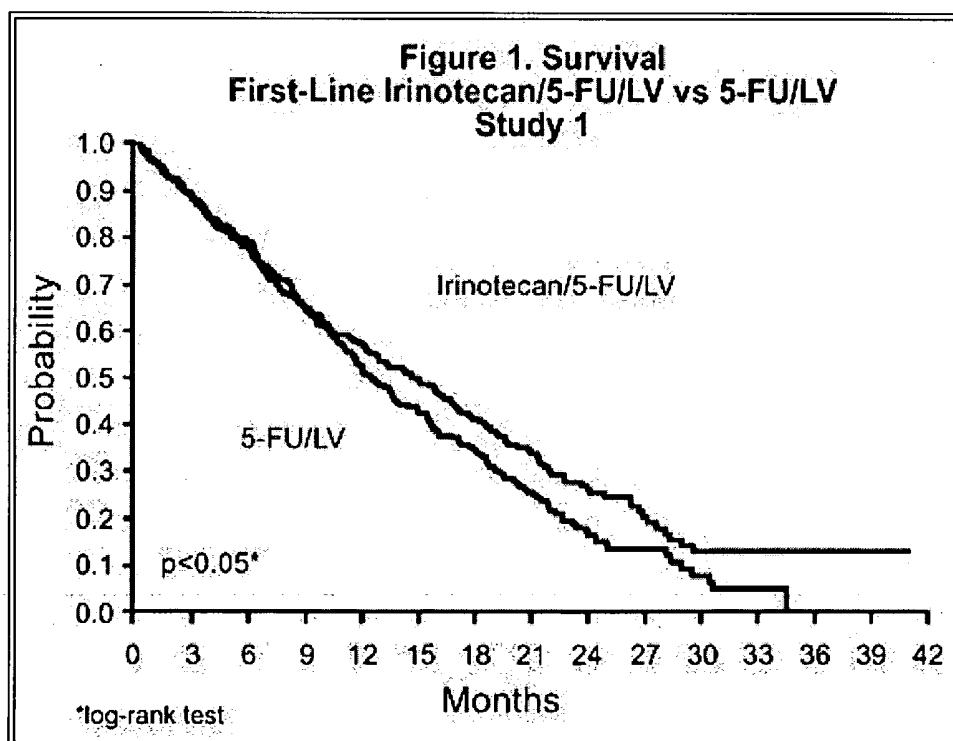
In both studies, the combination of irinotecan/5-FU/LV therapy resulted in significant improvements in objective tumor response rates, time to tumor progression, and survival when compared with 5-FU/LV alone. These differences in survival were observed in spite of second-line therapy in a majority of patients on both arms, including crossover to irinotecan-containing regimens in the control arm. Patient characteristics and major efficacy results are shown in Table 2.

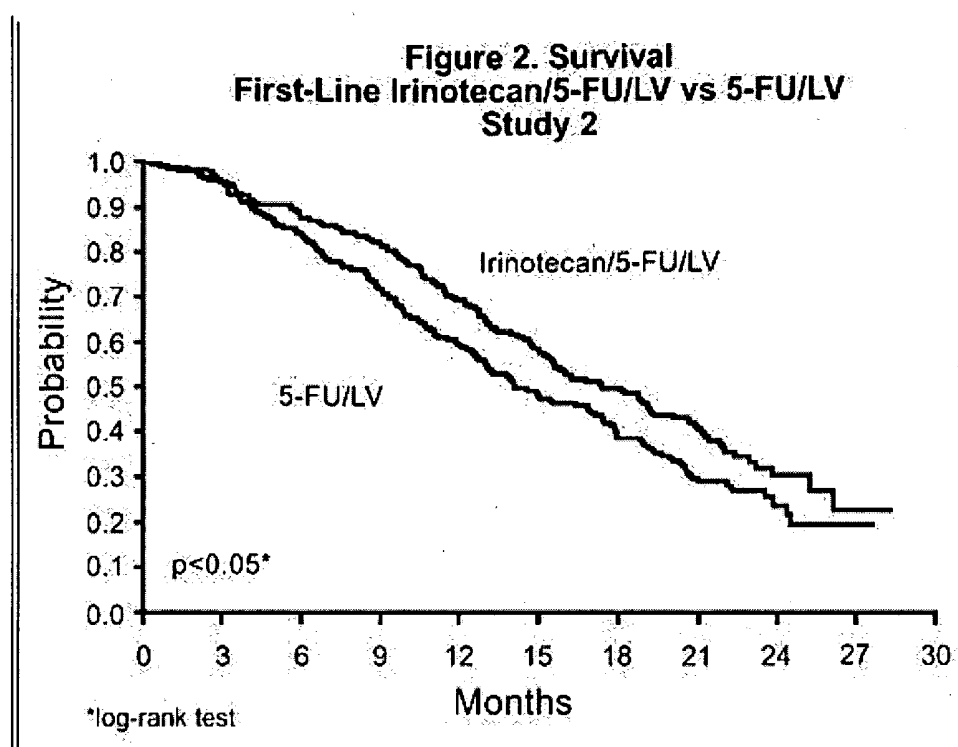
Table 2. Combination Dosage Schedule: Study Results

	Study 1			Study 2	
	Irinotecan + Bolus 5-FU/LV weekly × 4 q 6 weeks	Bolus 5-FU/LV daily × 5 q 4 weeks	Irinotecan weekly × 4 q 6 weeks	Irinotecan + Infusional 5-FU/LV	Infusional 5-FU
Number of Patients	231	226	226	198	18
Demographics and Treatment Administration					
Female/Male (%)	34/65	45/54	35/64	33/67	47/53
Median Age in years (range)	62 (25-85)	61 (19-85)	61 (30-87)	62 (27-75)	59 (27-85)
Performance Status (%)					
0	39	41	46	51	50
1	46	45	46	42	44
2	15	13	8	7	6
Primary Tumor (%)					
Colon	81	85	84	55	61
Rectum	17	14	15	45	39
Median Time from Diagnosis to Randomization (months, range)	1.9 (0-161)	1.7 (0-203)	1.8 (0.1-185)	4.5 (0-88)	2.1 (0-161)

Prior Adjuvant 5-FU Therapy (%)					
No	89	92	90	74	71
Yes	11	8	10	26	29
Median Duration of Study Treatment ^a					
(months)	5.5	4.1	3.9	5.6	4.1
Median Relative Dose Intensity (%) ^a					
Irinotecan	72	—	75	87	—
5-FU	71	86	—	86	93
Efficacy Results					
Confirmed Objective Tumor	39	21	18	35	27
Response Rate ^b (%)	(p<0.0001) ^c			(p<0.005) ^c	
Median Time to Tumor Progression ^d	7.0	4.3	4.2	6.7	4.1
(months)	(p=0.004) ^d			(p<0.001) ^d	
Median Survival	14.8	12.6	12.0	17.4	14.1
(months)	(p<0.05) ^d			(p<0.05) ^d	
^a Study 1: N=225 (irinotecan/5-FU/LV), N=219 (5-FU/LV), N=223 (irinotecan) Study 2: N=199 (irinotecan/5-FU/LV), N=186 (5-FU/LV)					
^b Confirmed ≥/4 to 6 weeks after first evidence of objective response					
^c Chi-square test					
^d Log-rank test					

Improvement was noted with irinotecan-based combination therapy relative to 5-FU/LV when response rates and time to tumor progression were examined across following demographic and disease-related subgroups (age, gender, ethnic origin, performance status, extent of organ involvement with cancer, time from diagnosis to cancer, prior adjuvant therapy, and baseline laboratory abnormalities). Figures 1 and 2 illustrate the Kaplan-Meier survival curves for the comparison of irinotecan/5-FU/LV versus 5-FU/LV in Studies 1 and 2, respectively.





Second-Line Treatment for Recurrent or Progressive Metastatic Colorectal Cancer After 5-FU-Based Treatment

Weekly Dosage Schedule

Data from three open-label, single-agent, clinical studies, involving a total of 304 patients in 59 centers, support the use of CAMPTOSAR in the treatment of patients with metastatic cancer of the colon or rectum that has recurred or progressed following treatment with 5-FU-based therapy. These studies were designed to evaluate tumor response rate and do not provide information on actual clinical benefit, such as effects on survival and disease-related symptoms. In each study, CAMPTOSAR was administered in repeated 6-week cycles consisting of a 90-minute intravenous infusion once weekly for 4 weeks, followed by a 2-week rest period. Starting doses of CAMPTOSAR in these trials were 100, 125, or 150 mg/m², but the 150-mg/m² dose was poorly tolerated (due to unacceptably high rates of grade 4 late diarrhea and febrile neutropenia). Study 1 enrolled 48 patients and was conducted by a single investigator at several regional hospitals. Study 2 was a multicenter study conducted by the North Central Cancer Treatment Group. All 90 patients enrolled in Study 2 received a starting dose of 125 mg/m². Study 3 was a multicenter study that enrolled 166 patients from 30 institutions. The initial dose in Study 3 was 125 mg/m² but was reduced to 100 mg/m² because the toxicity seen at the 125-mg/m² dose was perceived to be greater than that seen in previous studies. All patients in these studies had metastatic colorectal cancer, and the majority had disease that recurred or progressed following a 5-FU-based regimen administered for metastatic disease. The results of the individual studies are shown in Table 3.

Table 3. Weekly Dosage Schedule: Study Results

	Study			
	1	2	3	
Number of Patients	48	90	64	102
Starting Dose (mg/m ² /wk × 4)	125 ^a	125	125	100
Demographics and Treatment Administration				
Female/Male (%)	46/54	36/64	50/50	51/49
Median Age in years (range)	63 (29-78)	63 (32-81)	61 (42-84)	64 (25-84)
Ethnic Origin (%)				
White	79	96	81	91
African American	12	4	11	5
Hispanic	8	0	8	2
Oriental/Asian	0	0	0	2
Performance Status (%)				
0	60	38	59	44
1	38	48	33	51

2	2	14	8	5
Primary Tumor (%)				
Colon	100	71	89	87
Rectum	0	29	11	8
Unknown	0	0	0	5
Prior 5-FU Therapy (%)				
For Metastatic Disease	81	66	73	68
<= 6 months after Adjuvant	15	7	27	28
> 6 months after Adjuvant	2	16	0	2
Classification Unknown	2	12	0	3
Prior Pelvic/Abdominal Irradiation (%)				
Yes	3	29	0	0
Other	0	9	2	4
None	97	62	98	96
Duration of Treatment with CAMPTOSAR (median, months)	5	4	4	3
Relative Dose Intensity ^b (median %)	74	67	73	81
Efficacy				
Confirmed Objective Response Rate (%) ^c (95% CI)	21 (9.3-32.3)	13 (6.3-20.4)	14 (5.5-22.6)	9 (3.3-14.3)
Time to Response (median, months)	2.6	1.5	2.8	2.8
Response Duration (median, months)	6.4	5.9	5.6	6.4
Survival (median, months)	10.4	8.1	10.7	9.3
1-Year Survival (%)	46	31	45	43
^a Nine patients received 150 mg/m ² as a starting dose; two (22.2%) responded to CAMPTOSAR.				
^b Relative dose intensity for CAMPTOSAR based on planned dose intensity of 100, 83.3, and 66.7 mg/m ² /wk corresponding with 150, 125, and 100 mg/m ² starting doses, respectively.				
^c Confirmed >= 4 to 6 weeks after first evidence of objective response.				

In the intent-to-treat analysis of the pooled data across all three studies, 193 of the 304 patients began therapy at the recommended starting dose of 125 mg/m². Among these 193 patients, 2 complete and 27 partial responses were observed, for an overall response rate of 15.0% (95% Confidence Interval [CI], 10.0% to 20.0%) at this starting dose. A considerably lower response rate was seen with a starting dose of 100 mg/m². The majority of responses were observed within the first cycles of therapy, but responses did occur in later cycles of treatment (one response was observed after the eighth cycle). The median response duration for patients beginning therapy at 125 mg/m² was 5.8 months (range, 2.6 to 15.1 months). Of the 304 patients treated in the three studies, response rates to CAMPTOSAR similar in males and females and among patients older and younger than 65 years. Rates were also similar in patients with cancer of the colon or cancer of the rectum and in patients with single and multiple metastatic sites. The response rate was 18.5% in patients with a performance status of 0 and 8.2% in patients with a performance status of 1 or 2. Patients with a performance status of 3 or 4 have not been studied. Over half of the patients responding to CAMPTOSAR had not responded to prior 5-FU. Patients who had received previous irradiation to the pelvis responded to CAMPTOSAR at approximately the same rate as those who previously received irradiation.

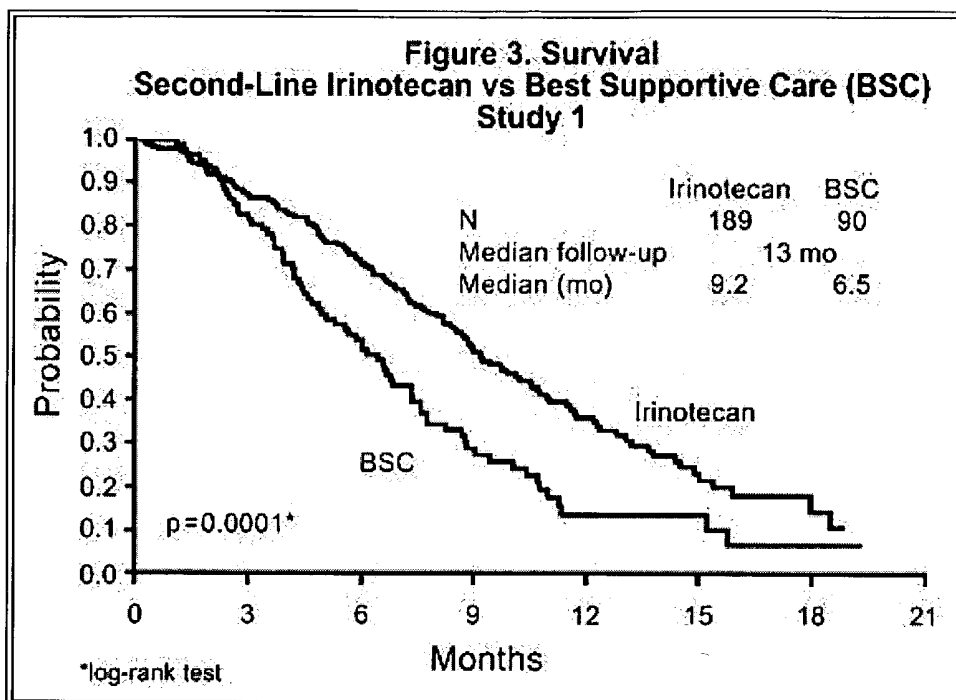
Once-Every-3-Week Dosage Schedule

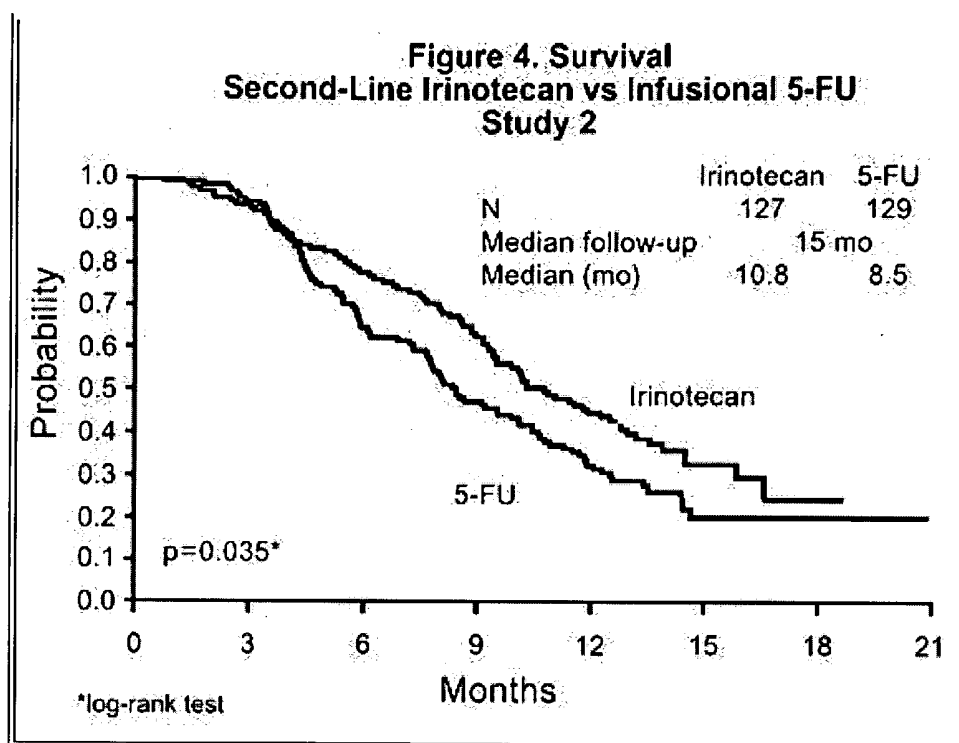
Single-Arm Studies: Data from an open-label, single-agent, single-arm, multicenter, clinical study involving a total of 132 patients support a once every-3-week schedule of irinotecan in the treatment of patients with metastatic cancer of the colon or rectum that recurred or progressed following treatment with 5-FU. Patients received a starting dose of 350 mg/m² given by 30-minute intravenous infusion once every 3 weeks. Among the 132 previously treated patients in this trial, the to-treat response rate was 12.1% (95% CI, 7.0% to 18.1%).

Randomized Trials: Two multicenter, randomized, clinical studies further support the use of irinotecan given by the once-every-3-week dosage schedule in patients with metastatic colorectal cancer whose disease has recurred or progressed following prior 5-FU therapy. In the first study, second-line irinotecan therapy plus supportive care was compared with best supportive care alone. In the second study, second-line irinotecan therapy was compared with infusional 5-FU-based therapy. In both studies, irinotecan was administered intravenously at a starting dose of 350 mg/m² over 90 minutes once every 3 weeks. The starting dose was 300 mg/m² for patients who were 70 years and older or who had a performance status of 2. The highest total dose permitted was 700 mg. Dose reductions and/or administrative delays were permitted in the event of severe hematologic and/or nonhematologic toxicities while on treatment. Best supportive care was provided to patients in the control arm of the second study and included antibiotics, analgesics, corticosteroids, transfusions, psychotherapy, or any other symptomatic therapy as clinically indicated. In the first study, concomitant medications such as antiemetics, atropine, and loperamide were given to patients for prophylaxis and/or management of symptoms from treatment. If late diarrhea persisted for greater than 24 hours despite loperamide, a 7-day course of fluoroquinolone antibiotic prophylaxis was given. Patients in the control arm of the second study received one of the following 5-FU regimens: (1) LV, 200 mg/m² IV over 2 hours; followed by 5-FU, 400 mg/m² IV bolus; followed by 5-FU, 600 mg/m² continuous IV infusion over 22 hours on days 1 and 2 every 2 weeks; (2) 5-FU, 250 to 300 mg/m²/day protracted continuous IV infusion until toxicity; (3) 5-FU, 2.6 to 3 g/m² IV over 24 hours every week for 6 weeks with or without LV, 20 to 500 mg/m²/day every week IV for 6 weeks with 2-week rest.

between cycles. Patients were to be followed every 3 to 6 weeks for 1 year.

A total of 535 patients were randomized in the two studies at 94 centers. The primary endpoint in both studies was survival. The studies demonstrated a significant overall survival advantage for irinotecan compared with best supportive care ($p=0.0001$) and infusional 5-FU-based therapy ($p=0.035$) as shown in Figures 3 and 4. In Study 1, median survival for patients treated with irinotecan was 9.2 months compared with 6.5 months for patients receiving best supportive care. In Study 2, median survival for patients treated with irinotecan was 10.8 months compared with 8.5 months for patients receiving infusional 5-FU-based therapy. Multiple regression analyses determined that patients' baseline characteristics also had a significant effect on survival. When adjusted for performance status and other baseline prognostic factors, survival among patients treated with irinotecan remained significantly longer than in the control populations ($p=0.001$ for Study 1 and $p=0.01$ for Study 2). Measurements of pain, performance status, and weight loss were collected prospectively in the two studies; however, the plan for the analysis of these was defined retrospectively. When comparing irinotecan with best supportive care in Study 1, this analysis showed a statistically significant advantage for irinotecan with longer time to development of pain (6.9 months versus 2.0 months), time to performance status deterioration (5.7 months versus 3.3 months), and time to weight loss (6.4 months versus 4.2 months). Additionally, 33.3% (33/99) of patients with a baseline performance status of 1 or 2 showed an improvement in performance status when treated with irinotecan versus 11.3% (7/62) of patients receiving best supportive care ($p=0.002$). Because of the inclusion of patients with non-measurable disease, intent-to-treat response rates could not be assessed.





In the two randomized studies, the EORTC QLQ-C30 instrument was utilized. At the start of each cycle of therapy, patients completed a questionnaire consisting of questions, such as "Did pain interfere with daily activities?" (1 = Not at All, to 4 = Very Much) and "Do you have any trouble taking a long walk?" (Yes or No). The answers from the 30 questions were converted into 15 subscales, that were scored from 0 to 100, and the global health status subscale that was derived from questions about the patient's sense of general well being in the past week. In addition to the global health status subscale, there were five functional (i.e., cognitive, emotional, social, physical, role) and nine symptom (i.e., fatigue, appetite loss, pain assessment, insomnia, constipation, dyspnea, nausea/vomiting, financial impact, diarrhea) subscales. The results as summarized in Table 5 are based on patients' worst post-baseline scores. In Study 1, a multivariate analysis and univariate analyses of the individual subscales were performed and corrected for multivariate testing. Patients receiving irinotecan reported significantly better results for global health status, on two of five functional subscales, and on four of nine symptom subscales. As expected, patients receiving irinotecan noted significantly less diarrhea than those receiving best supportive care. In Study 2, the multivariate analysis on all 15 subscales did not indicate a statistically significant difference between irinotecan and infusional 5-FU.

Table 4. Once-Every-3-Week Dosage Schedule: Study Results

	Study 1		Study 2	
	Irinotecan	BSC ^a	Irinotecan	5-FU
Number of Patients	189	90	127	129
Demographics and Treatment Administration				
Female/Male (%)	32/68	42/58	43/57	35/65
Median Age in years (range)	59 (22-75)	62 (34-75)	58 (30-75)	58 (25-75)
Performance Status (%)				
0	47	31	58	54
1	39	46	35	43
2	14	23	8	3
Primary Tumor (%)				
Colon	55	52	57	62
Rectum	45	48	43	38
Prior 5-FU Therapy (%)				
For Metastatic Disease	70	63	58	68
As Adjuvant Treatment	30	37	42	32
Prior Irradiation (%)	26	27	18	20
Duration of Study Treatment				
(median, months)	4.1	—	4.2	2.8
(Log-rank test)			(p=0.02)	
Relative Dose Intensity				

(median %) ^b	94	–	95	81-99
Survival				
Survival (median, months)	9.2	6.5	10.8	8.5
(Log-rank test)	(p=0.0001)		(p=0.035)	
^a BSC = best supportive care				
^b Relative dose intensity for irinotecan based on planned dose intensity of 116.7 and 100 mg/m ² /wk corresponding with 350 and 300 mg/m ² starting doses, respectively.				

Table 5. EORTC QLQ-C30: Mean Worst Post-Baseline Score ^a

QLQ-C30 Subscale	Study 1			Study 2		
	Irinotecan	BSC	p-value	Irinotecan	5-FU	p-value
Global Health Status	47	37	0.03	53	52	0.9
Functional Scales						
Cognitive	77	68	0.07	79	83	0.9
Emotional	68	64	0.4	64	68	0.9
Social	58	47	0.06	65	67	0.9
Physical	60	40	0.0003	66	66	0.9
Role	53	35	0.02	54	57	0.9
Symptom Scales						
Fatigue	51	63	0.03	47	46	0.9
Appetite Loss	37	57	0.0007	35	38	0.9
Pain Assessment	41	56	0.009	38	34	0.9
Insomnia	39	47	0.3	39	33	0.9
Constipation	28	41	0.03	25	19	0.9
Dyspnea	31	40	0.2	25	24	0.9
Nausea/Vomiting	27	29	0.5	25	16	0.09
Financial Impact	22	26	0.5	24	15	0.3
Diarrhea	32	19	0.01	32	22	0.2

^a For the five functional subscales and global health status subscale, higher scores imply better functioning, whereas, on the nine symptom subscales, higher scores imply more severe symptoms. The subscale scores of each patient were collected at each visit until the patient dropped out of the study.

INDICATIONS AND USAGE

CAMPTOSAR Injection is indicated as a component of first-line therapy in combination with 5-fluorouracil and leucovorin for patients with metastatic carcinoma colon or rectum. CAMPTOSAR is also indicated for patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed follow fluorouracil-based therapy.

CONTRAINDICATIONS

CAMPTOSAR Injection is contraindicated in patients with a known hypersensitivity to the drug.

WARNINGS

General

Outside of a well-designed clinical study, CAMPTOSAR Injection should not be used in combination with the "Mayo Clinic" regimen of 5-FU/LV (administration consecutive days every 4 weeks) because of reports of increased toxicity, including toxic deaths. CAMPTOSAR should be used as recommended (see DOSAGE ADMINISTRATION, Table 10).

In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle tri discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with a baseline performance status of 0 or

Diarrhea

CAMPTOSAR can induce both early and late forms of diarrhea that appear to be mediated by different mechanisms. Early diarrhea (occurring during or shortly after infusion of CAMPTOSAR) is cholinergic in nature. It is usually transient and only infrequently is severe. It may be accompanied by symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyper-peristalsis that can cause abdominal cramping. Early diarrhea and other cholinergic symptoms may be prevented or ameliorated by administration of atropine (see PRECAUTIONS, General, for dosing recommendations for atropine).

Late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) can be life threatening since it may be prolonged and may lead to dehydration, electrolyte imbalance, or sepsis. Late diarrhea should be treated promptly with loperamide (see PRECAUTIONS, Information for Patients, for dosing recommendations for loperamide). Patients with diarrhea should be carefully monitored, should be given fluid and electrolyte replacement if they become dehydrated and should be given antibiotic support if they develop ileus, fever, or severe neutropenia. After the first treatment, subsequent weekly chemotherapy treatments should be delayed in patients until return of pretreatment bowel function for at least 24 hours without need for antidiarrhea medication. If grade 2, 3, or 4 late diarrhea occurs, subsequent doses of CAMPTOSAR should be decreased within the current cycle (see DOSAGE AND ADMINISTRATION).

Neutropenia

Deaths due to sepsis following severe neutropenia have been reported in patients treated with CAMPTOSAR. Neutropenic complications should be managed with antibiotic support (see PRECAUTIONS). Therapy with CAMPTOSAR should be temporarily omitted during a cycle of therapy if neutropenic fever occurs (absolute neutrophil count drops $<1000/\text{mm}^3$). After the patient recovers to an absolute neutrophil count $\geq 1000/\text{mm}^3$, subsequent doses of CAMPTOSAR should be reduced depending upon the level of neutropenia observed (see DOSAGE AND ADMINISTRATION).

Routine administration of a colony-stimulating factor (CSF) is not necessary, but physicians may wish to consider CSF use in individual patients experiencing severe neutropenia.

Hypersensitivity

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have been observed.

Colitis/Ileus

Cases of colitis complicated by ulceration, bleeding, ileus, and infection have been observed. Patients experiencing ileus should receive prompt antibiotic support (see PRECAUTIONS).

Renal Impairment/Renal Failure

Rare cases of renal impairment and acute renal failure have been identified, usually in patients who became volume depleted from severe vomiting and/or diarrhea.

Thromboembolism

Thromboembolic events have been observed in patients receiving irinotecan-containing regimens; the specific cause of these events has not been determined.

Pregnancy

CAMPTOSAR may cause fetal harm when administered to a pregnant woman. Radioactivity related to ^{14}C -irinotecan crosses the placenta of rats following intravenous administration of 10 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 3 and 0.5 times, respectively, the corresponding values in patients administered 125 mg/m²). Administration of 6 mg/kg/day intravenous irinotecan to rats (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.2 times, respectively, the corresponding values in patients administered 125 mg/m²) and rabbits (about one-half the recommended human starting dose on a mg/m² basis) during the period of organogenesis, is embryotoxic as characterized by increased post-implantation loss and decreased number of live fetuses. Irinotecan was teratogenic in rats at doses greater than 1.2 mg/kg/day (which in separate studies produced an irinotecan C_{max} and AUC about 2 and 0.1/40th, respectively, of the corresponding values in patients administered 125 mg/m²) and in rabbits at 6.0 mg/kg/day (about one-half the recommended human starting dose on a mg/m² basis). Teratogenic effects included a variety of external, visceral, and skeletal abnormalities. Irinotecan administered to rats during the period following organogenesis through weaning at doses of 6 mg/kg/day caused decreased learning ability and decreased female body weights in the offspring. There are no adequate and well-controlled studies of irinotecan in pregnant women. If the drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with CAMPTOSAR.

PRECAUTIONS

General

Care of Intravenous Site: CAMPTOSAR Injection is administered by intravenous infusion. Care should be taken to avoid extravasation, and the infusion site should be monitored for signs of inflammation. Should extravasation occur, flushing the site with sterile water and applications of ice are recommended.

Premedication with Antiemetics: Irinotecan is emetogenic. It is recommended that patients receive premedication with antiemetic agents. In clinical studies of

weekly dosage schedule, the majority of patients received 10 mg of dexamethasone given in conjunction with another type of antiemetic agent, such as a 5-HT blocker (e.g., ondansetron or granisetron). Antiemetic agents should be given on the day of treatment, starting at least 30 minutes before administration of CAMPTOSAR. Physicians should also consider providing patients with an antiemetic regimen (e.g., prochlorperazine) for subsequent use as needed.

Treatment of Cholinergic Symptoms: Prophylactic or therapeutic administration of 0.25 to 1 mg of intravenous or subcutaneous atropine should be considered (clinically contraindicated) in patients experiencing rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping, or diarrhea (occurring during or shortly after infusion of CAMPTOSAR). These symptoms are expected to occur more frequently with higher irinotecan doses.

Patients at Particular Risk: In patients receiving either irinotecan/5-FU/LV or 5-FU/LV in the clinical trials, higher rates of hospitalization, neutropenic fever, thromboembolism, first-cycle treatment discontinuation, and early deaths were observed in patients with a baseline performance status of 2 than in patients with baseline performance status of 0 or 1. Patients who had previously received pelvic/abdominal radiation and elderly patients with comorbid conditions should be monitored.

The use of CAMPTOSAR in patients with significant hepatic dysfunction has not been established. In clinical trials of either dosing schedule, irinotecan was not administered to patients with serum bilirubin >2.0 mg/dL, or transaminase >3 times the upper limit of normal if no liver metastasis, or transaminase >5 times the limit of normal with liver metastasis. However in clinical trials of the weekly dosage schedule, it has been noted that patients with modestly elevated baseline serum total bilirubin levels (1.0 to 2.0 mg/dL) have had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels less than 1.0 mg/dL (50.0% [19/38] versus 17.7% [47/226]; $p < 0.001$). Patients with abnormal glucuronidation of bilirubin, such as those with Gilbert's syndrome, may also be at greater risk of myelosuppression when receiving therapy with CAMPTOSAR. An association between baseline bilirubin elevations and an increase in late diarrhea has not been observed in studies of the weekly dosage schedule.

Information for Patients

Patients and patients' caregivers should be informed of the expected toxic effects of CAMPTOSAR, particularly of its gastrointestinal complications, such as nausea, vomiting, abdominal cramping, diarrhea, and infection. Each patient should be instructed to have loperamide readily available and to begin treatment for late diarrhea (generally occurring more than 24 hours after administration of CAMPTOSAR) at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. One dosage regimen for loperamide used in clinical trials consisted of the following (Note: This dosage regimen exceeds the usual dosage recommendations for loperamide.): 4 mg at the first onset of late diarrhea and then 2 mg every 2 hours until the patient is diarrhea-free for at least 12 hours. During the night, the patient may take 4 mg of loperamide every 4 hours. Premedication with loperamide is not recommended. Use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

Patients should be instructed to contact their physician or nurse if any of the following occur: diarrhea for the first time during treatment; black or bloody stools; symptoms of dehydration such as lightheadedness, dizziness, or faintness; inability to take fluids by mouth due to nausea or vomiting; inability to get diarrhea under control within 24 hours; or fever or evidence of infection.

Patients should be alerted to the possibility of alopecia.

Laboratory Tests

Careful monitoring of the white blood cell count with differential, hemoglobin, and platelet count is recommended before each dose of CAMPTOSAR.

Drug Interactions

The adverse effects of CAMPTOSAR, such as myelosuppression and diarrhea, would be expected to be exacerbated by other antineoplastic agents having similar adverse effects.

Patients who have previously received pelvic/abdominal irradiation are at increased risk of severe myelosuppression following the administration of CAMPTOSAR. Concurrent administration of CAMPTOSAR with irradiation has not been adequately studied and is not recommended.

Lymphocytopenia has been reported in patients receiving CAMPTOSAR, and it is possible that the administration of dexamethasone as antiemetic prophylaxis has enhanced the likelihood of this effect. However, serious opportunistic infections have not been observed, and no complications have specifically been attributed to lymphocytopenia.

Hyperglycemia has also been reported in patients receiving CAMPTOSAR. Usually, this has been observed in patients with a history of diabetes mellitus or evidence of glucose intolerance prior to administration of CAMPTOSAR. It is probable that dexamethasone, given as antiemetic prophylaxis, contributed to hyperglycemia in these patients.

The incidence of akathisia in clinical trials of the weekly dosage schedule was greater (8.5%, 4/47 patients) when prochlorperazine was administered on the same day as CAMPTOSAR than when these drugs were given on separate days (1.3%, 1/80 patients). The 8.5% incidence of akathisia, however, is within the range reported for the use of prochlorperazine when given as a premedication for other chemotherapies.

It would be expected that laxative use during therapy with CAMPTOSAR would worsen the incidence or severity of diarrhea, but this has not been studied.

In view of the potential risk of dehydration secondary to vomiting and/or diarrhea induced by CAMPTOSAR, the physician may wish to withhold diuretics during therapy with CAMPTOSAR and, certainly, during periods of active vomiting or diarrhea.

Drug-Laboratory Test Interactions

There are no known interactions between CAMPTOSAR and laboratory tests.

Carcinogenesis, Mutagenesis & Impairment of Fertility

Long-term carcinogenicity studies with irinotecan were not conducted. Rats were, however, administered intravenous doses of 2 mg/kg or 25 mg/kg irinotecan week for 13 weeks (in separate studies, the 25 mg/kg dose produced an irinotecan C_{max} and AUC that were about 7.0 times and 1.3 times the respective values in patients administered 125 mg/m² weekly) and were then allowed to recover for 91 weeks. Under these conditions, there was a significant linear trend with dose of incidence of combined uterine horn endometrial stromal polyps and endometrial stromal sarcomas. Neither irinotecan nor SN-38 was mutagenic in the in vitro / assay. Irinotecan was clastogenic both in vitro (chromosome aberrations in Chinese hamster ovary cells) and in vivo (micronucleus test in mice). No significant effects on fertility and general reproductive performance were observed after intravenous administration of irinotecan in doses of up to 6 mg/kg/day to rats and dogs. However, atrophy of male reproductive organs was observed after multiple daily irinotecan doses both in rodents at 20 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about 5 and 1 times, respectively, the corresponding values in patients administered 125 mg/m² weekly) and dogs at 0.4 mg/kg (which in separate studies produced an irinotecan C_{max} and AUC about one-half and 1/15th, respectively, the corresponding values in patients administered 125 mg/m² weekly).

Pregnancy

Pregnancy Category D—see WARNINGS.

Nursing Mothers

Radioactivity appeared in rat milk within 5 minutes of intravenous administration of radiolabeled irinotecan and was concentrated up to 65-fold at 4 hours after administration relative to plasma concentrations. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in infants, it is recommended that nursing be discontinued when receiving therapy with CAMPTOSAR.

Pediatric Use

The safety and effectiveness of CAMPTOSAR in pediatric patients have not been established.

Geriatric Use

Patients greater than 65 years of age should be closely monitored because of a greater risk of late diarrhea in this population (see CLINICAL PHARMACOLOGY: Pharmacokinetics in Special Populations and ADVERSE REACTIONS, Overview of Adverse Events). The starting dose of CAMPTOSAR in patients 70 years of age or older for the once-every-3-week-dosage schedule should be 300 mg/m² (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

First-Line Combination Therapy

A total of 955 patients with metastatic colorectal cancer received the recommended regimens of irinotecan in combination with 5-FU/LV, 5-FU/LV alone, or irinotecan alone. In the two phase 3 studies, 370 patients received irinotecan in combination with 5-FU/LV, 362 patients received 5-FU/LV alone, and 223 patients received irinotecan alone. (See Table 10 in DOSAGE AND ADMINISTRATION for recommended combination-agent regimens.)

In Study 1, 49 (7.3%) patients died within 30 days of last study treatment: 21 (9.3%) received irinotecan in combination with 5-FU/LV, 15 (6.8%) received 5-FU/LV alone, and 13 (5.8%) received irinotecan alone. Deaths potentially related to treatment occurred in 2 (0.9%) patients who received irinotecan in combination with 5-FU/LV (2 neutropenic fever/sepsis), 3 (1.4%) patients who received 5-FU/LV alone (1 neutropenic fever/sepsis, 1 CNS bleeding during thrombocytopenia, 1 unknown), and 2 (0.9%) patients who received irinotecan alone (2 neutropenic fever). Deaths from any cause within 60 days of first study treatment were reported for 15 (3.8%) patients who received irinotecan in combination with 5-FU/LV, 16 (7.3%) patients who received 5-FU/LV alone, and 15 (6.7%) patients who received irinotecan alone. Discontinuations due to adverse events were reported for 17 (7.6%) patients who received irinotecan in combination with 5-FU/LV, 14 (6.4%) patients who received 5-FU/LV alone, and 26 (11.7%) patients who received irinotecan alone.

In Study 2, 10 (3.5%) patients died within 30 days of last study treatment: 6 (4.1%) received irinotecan in combination with 5-FU/LV and 4 (2.8%) received 5-FU/LV alone. There was one potentially treatment-related death, which occurred in a patient who received irinotecan in combination with 5-FU/LV (0.7%, neutropenic fever). Deaths from any cause within 60 days of first study treatment were reported for 3 (2.1%) patients who received irinotecan in combination with 5-FU/LV and 2 (0.7%) patients who received 5-FU/LV alone. Discontinuations due to adverse events were reported for 9 (6.2%) patients who received irinotecan in combination with 5-FU/LV and 1 (0.7%) patient who received 5-FU/LV alone.

The most clinically significant adverse events for patients receiving irinotecan-based therapy were diarrhea, nausea, vomiting, neutropenia, and alopecia. The most clinically significant adverse events for patients receiving 5-FU/LV therapy were diarrhea, neutropenia, neutropenic fever, and mucositis. In Study 1, grade 4 neutropenia, neutropenic fever (defined as grade 2 fever and grade 4 neutropenia), and mucositis were observed less often with weekly irinotecan/5-FU/LV than with the monthly administration of 5-FU/LV.

Tables 6 and 7 list the clinically relevant adverse events reported in Studies 1 and 2, respectively.

Table 6. Study 1: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies ^a

Adverse Event	Study 1					
	Irinotecan + Bolus 5-FU/LV weekly × 4 q 6 weeks N=225		Bolus 5-FU/LV daily × 5 q 4 weeks N=219		Irinotecan weekly × 4 q 6 weeks N=223	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3
TOTAL Adverse Events	100	53.3	100	45.7	99.6	45.7
GASTROINTESTINAL						
Diarrhea						
late	84.9	22.7	69.4	13.2	83.0	31.0
grade 3	--	15.1	--	5.9	--	18.4
grade 4	--	7.6	--	7.3	--	12.6
early	45.8	4.9	31.5	1.4	43.0	6.7
Nausea	79.1	15.6	67.6	8.2	81.6	16.1
Abdominal pain	63.1	14.6	50.2	11.5	67.7	13.0
Vomiting	60.4	9.7	46.1	4.1	62.8	12.1
Anorexia	34.2	5.8	42.0	3.7	43.9	7.2
Constipation	41.3	3.1	31.5	1.8	32.3	0.4
Mucositis	32.4	2.2	76.3	16.9	29.6	2.2
HEMATOLOGIC						
Neutropenia	96.9	53.8	98.6	66.7	96.4	31.4
grade 3	--	29.8	--	23.7	--	19.3
grade 4	--	24.0	--	42.5	--	12.1
Leukopenia	96.9	37.8	98.6	23.3	96.4	21.5
Anemia	96.9	8.4	98.6	5.5	96.9	4.5
Neutropenic fever	--	7.1	--	14.6	--	5.8
Thrombocytopenia	96.0	2.6	98.6	2.7	96.0	1.7
Neutropenic infection	--	1.8	--	0	--	2.2
BODY AS A WHOLE						
Asthenia	70.2	19.5	64.4	11.9	69.1	13.9
Pain	30.7	3.1	26.9	3.6	22.9	2.2
Fever	42.2	1.7	32.4	3.6	43.5	0.4
Infection	22.2	0	16.0	1.4	13.9	0.4
METABOLIC & NUTRITIONAL						
up Bilirubin	87.6	7.1	92.2	8.2	83.9	7.2
DERMATOLOGIC						
Exfoliative dermatitis	0.9	0	3.2	0.5	0	0
Rash	19.1	0	26.5	0.9	14.3	0.4
Alopecia ^b	43.1	--	26.5	--	46.1	--
RESPIRATORY						
Dyspnea	27.6	6.3	16.0	0.5	22.0	2.2
Cough	26.7	1.3	18.3	0	20.2	0.4
Pneumonia	6.2	2.7	1.4	1.0	3.6	1.3
NEUROLOGIC						
Dizziness	23.1	1.3	16.4	0	21.1	1.8
Somnolence	12.4	1.8	4.6	1.8	9.4	1.3
Confusion	7.1	1.8	4.1	0	2.7	0
CARDIOVASCULAR						
Vasodilation	9.3	0.9	5.0	0	9.0	0

Hypotension	5.8	1.3	2.3	0.5	5.8	1.7
Thromboembolic events ^c	9.3	—	11.4	—	5.4	—

^a Severity of adverse events based on NCI CTC (version 1.0)

^b Complete hair loss = Grade 2

^c Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest, myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.

Table 7. Study 2: Percent (%) of Patients Experiencing Clinically Relevant Adverse Events in Combination Therapies ^a

Adverse Event	Study 2			
	Irinotecan + 5-FU/LV Infusional d 1&2 q 2 weeks N=145		5-FU/LV Infusional d 1&2 q 2 weeks N=143	
	Grade 1-4	Grade 3&4	Grade 1-4	Grade 3&4
TOTAL Adverse Events	100	72.4	100	39.2
GASTROINTESTINAL				
Diarrhea late	72.4	14.4	44.8	6.3
grade 3	—	10.3	—	4.2
grade 4	—	4.1	—	2.1
Cholinergic syndrome ^b	28.3	1.4	0.7	0
Nausea	66.9	2.1	55.2	3.5
Abdominal pain	17.2	2.1	16.8	0.7
Vomiting	44.8	3.5	32.2	2.8
Anorexia	35.2	2.1	18.9	0.7
Constipation	30.3	0.7	25.2	1.4
Mucositis	40.0	4.1	28.7	2.8
HEMATOLOGIC				
Neutropenia	82.5	46.2	47.9	13.4
grade 3	—	36.4	—	12.7
grade 4	—	9.8	—	0.7
Leukopenia	81.3	17.4	42.0	3.5
Anemia	97.2	2.1	90.9	2.1
Neutropenic fever	—	3.4	—	0.7
Thrombocytopenia	32.6	0	32.2	0
Neutropenic infection	—	2.1	—	0
BODY AS A WHOLE				
Asthenia	57.9	9.0	48.3	4.2
Pain	64.1	9.7	61.5	8.4
Fever	22.1	0.7	25.9	0.7
Infection	35.9	7.6	33.6	3.5
METABOLIC & NUTRITIONAL				
up Bilirubin	19.1	3.5	35.9	10.6
DERMATOLOGIC				
Hand & foot syndrome	10.3	0.7	12.6	0.7
Cutaneous signs	17.2	0.7	20.3	0
Alopecia ^c	56.6	—	16.8	—
RESPIRATORY				
Dyspnea	9.7	1.4	4.9	0
CARDIOVASCULAR				
Hypotension	3.4	1.4	0.7	0
	11.7	—	5.6	—

Thromboembolic events ^d				
^a Severity of adverse events based on NCI CTC (version 1.0)				
^b Includes rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, abdominal cramping or diarrhea (occurring during or shortly after infusion of irinotecan).				
^c Complete hair loss = Grade 2				
^d Includes angina pectoris, arterial thrombosis, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, embolus lower extremity, heart arrest myocardial infarct, myocardial ischemia, peripheral vascular disorder, pulmonary embolus, sudden death, thrombophlebitis, thrombosis, vascular disorder.				

Second-Line Single-Agent Therapy

Weekly Dosage Schedule

In three clinical studies evaluating the weekly dosage schedule, 304 patients with metastatic carcinoma of the colon or rectum that had recurred or progressed 5-FU-based therapy were treated with CAMPTOSAR. Seventeen of the patients died within 30 days of the administration of CAMPTOSAR; in five cases (1.6%) the deaths were potentially drug-related. These five patients experienced a constellation of medical events that included known effects of CAMPTOSAR. One patient died of neutropenic sepsis without fever. Neutropenic fever occurred in nine (3.0%) other patients; these patients recovered with supportive care.

One hundred nineteen (39.1%) of the 304 patients were hospitalized a total of 156 times because of adverse events; 81 (26.6%) patients were hospitalized for judged to be related to administration of CAMPTOSAR. The primary reasons for drug-related hospitalization were diarrhea, with or without nausea and/or vomit (18.4%); neutropenia/leukopenia, with or without diarrhea and/or fever (8.2%); and nausea and/or vomiting (4.9%).

Table 8. Adverse Events Occurring in >10% of 304 Previously Treated Patients with Metastatic Carcinoma of the Colon or Rectum ^a		
Body System & Event	% of Patients Reporting	
NCI Grades 1-4	NCI Grades 3 & 4	
GASTROINTESTINAL		
Diarrhea (late) ^b	88	31
7-9 stools/day (grade 3)	—	(16)
>10 stools/day (grade 4)	—	(14)
Nausea	86	17
Vomiting	67	12
Anorexia	55	6
Diarrhea (early) ^c	51	8
Constipation	30	2
Flatulence	12	0
Stomatitis	12	1
Dyspepsia	10	0
HEMATOLOGIC		
Leukopenia	63	28
Anemia	60	7
Neutropenia	54	26
500 to <1000/mm ³ (grade 3)	—	(15)
<500/mm ³ (grade 4)	—	(12)
BODY AS A WHOLE		
Asthenia	76	12
Abdominal cramping/pain	57	16
Fever	45	1
Pain	24	2
Headache	17	1
Back pain	14	2
Chills	14	0

Minor infection ^d	14	0
Edema	10	1
Abdominal Enlargement	10	0
METABOLIC & NUTRITIONAL		
down Body weight	30	1
Dehydration	15	4
up Alkaline phosphatase	13	4
up SGOT	10	1
DERMATOLOGIC		
Alopecia	60	NA ^e
Sweating	16	0
Rash	13	1
RESPIRATORY		
Dyspnea	22	4
up Coughing	17	0
Rhinitis	16	0
NEUROLOGIC		
Insomnia	19	0
Dizziness	15	0
CARDIOVASCULAR		
Vasodilation (flushing)	11	0
^a Severity of adverse events based on NCI CTC (version 1.0)		
^b Occurring >24 hours after administration of CAMPTOSAR		
^c Occurring ≤24 hours after administration of CAMPTOSAR		
^d Primarily upper respiratory infections		
^e Not applicable; complete hair loss = NCI grade 2		

**Table 9. Percent of Patients Experiencing Grade 3 & 4
Adverse Events in Comparative Studies of
Once-Every-3-Week Irinotecan Therapy ^a**

Adverse Event	Study 1		Study 2	
	Irinotecan N=189	BSC ^b N=90	Irinotecan N=127	5-FU N=129
TOTAL Grade 3/4				
Adverse Events	79	67	69	54
GASTROINTESTINAL				
Diarrhea	22	6	22	11
Vomiting	14	8	14	5
Nausea	14	3	11	4
Abdominal pain	14	16	9	8
Constipation	10	8	8	6
Anorexia	5	7	6	4
Mucositis	2	1	2	5
HEMATOLOGIC				
Leukopenia/ Neutropenia	22	0	14	2
Anemia	7	6	6	3
Hemorrhage	5	3	1	3
Thrombocytopenia	1	0	4	2
Infection				
without grade 3/4 neutropenia	8	3	1	4
with grade 3/4				

neutropenia	1	0	2	0
Fever				
without grade 3/4 neutropenia	2	1	2	0
with grade 3/4 neutropenia	2	0	4	2
BODY AS A WHOLE				
Pain	19	22	17	13
Asthenia	15	19	13	12
METABOLIC & NUTRITIONAL				
Hepatic ^c	9	7	9	6
DERMATOLOGIC				
Hand & foot syndrome	0	0	0	5
Cutaneous signs ^d	2	0	1	3
RESPIRATORY ^e	10	8	5	7
NEUROLOGIC ^f	12	13	9	4
CARDIOVASCULAR ^g	9	3	4	2
OTHER ^h	32	28	12	14
^a Severity of adverse events based on NCI CTC (version 1.0)				
^b BSC = best supportive care				
^c Hepatic includes events such as ascites and jaundice				
^d Cutaneous signs include events such as rash				
^e Respiratory includes events such as dyspnea and cough				
^f Neurologic includes events such as somnolence				
^g Cardiovascular includes events such as dysrhythmias, ischemia, and mechanical cardiac dysfunction				
^h Other includes events such as accidental injury, hepatomegaly, syncope, vertigo, and weight loss				

Adjustments in the dose of CAMPTOSAR were made during the cycle of treatment and for subsequent cycles based on individual patient tolerance. The first or at least one cycle of CAMPTOSAR was reduced for 67% of patients who began the studies at the 125-mg/m² starting dose. Within-cycle dose reductions were made for 32% of the cycles initiated at the 125-mg/m² dose level. The most common reasons for dose reduction were late diarrhea, neutropenia, and leukopenia. Thirteen (4.3%) patients discontinued treatment with CAMPTOSAR because of adverse events. The adverse events in Table 8 are based on the experience of the 304 enrolled in the three studies described in the CLINICAL STUDIES, Studies Evaluating the Weekly Dosage Schedule, section.

Once-Every-3-Week Dosage Schedule

A total of 535 patients with metastatic colorectal cancer whose disease had recurred or progressed following prior 5-FU therapy participated in the two phase 3 studies. 316 received irinotecan, 129 received 5-FU, and 90 received best supportive care. Eleven (3.5%) patients treated with irinotecan died within 30 days of treatment; three cases (1%, 3/316), the deaths were potentially related to irinotecan treatment and were attributed to neutropenic infection, grade 4 diarrhea, and asthenia, respectively. One (0.8%, 1/129) patient treated with 5-FU died within 30 days of treatment; this death was attributed to grade 4 diarrhea.

Hospitalizations due to serious adverse events (whether or not related to study treatment) occurred at least once in 60% (188/316) of patients who received irinotecan, 63% (57/90) who received best supportive care, and 39% (50/129) who received 5-FU-based therapy. Eight percent of patients treated with irinotecan and 7% with 5-FU-based therapy discontinued treatment due to adverse events.

Of the 316 patients treated with irinotecan, the most clinically significant adverse events (all grades, 1-4) were diarrhea (84%), alopecia (72%), nausea (70%), vomiting (62%), cholinergic symptoms (47%), and neutropenia (30%). Table 9 lists the grade 3 and 4 adverse events reported in the patients enrolled to all treatment arms in the two studies described in the CLINICAL STUDIES, Studies Evaluating the Once-Every-3-Week Dosage Schedule, section.

Overview of Adverse Events

Gastrointestinal: Nausea, vomiting, and diarrhea are common adverse events following treatment with CAMPTOSAR and can be severe. When observed, nausea and vomiting usually occur during or shortly after infusion of CAMPTOSAR. In the clinical studies testing the every 3-week dosage schedule, the median time to onset of late diarrhea was 5 days after irinotecan infusion. In the clinical studies evaluating the weekly dosage schedule, the median time to onset of late diarrhea was 4 days following administration of CAMPTOSAR. For patients starting treatment at the 125-mg/m² weekly dose, the median duration of any grade of late diarrhea was 7 days. Among those patients treated at the 125-mg/m² weekly dose who experienced grade 3 or 4 late diarrhea, the median duration of the entire episode of diarrhea was 7 days. The frequency of grade 3 or 4 late diarrhea was somewhat greater in patients starting treatment at 125 mg/m² than in patients given a 100-mg/m² starting dose (34% [65/193] versus 23% [24/102]; p=0.08). The frequency of grade 3 and 4 late diarrhea by age was significantly greater in patients ≥65 year

patients <65 years (40% [53/133] versus 23% [40/171]; $p=0.002$). In one study of the weekly dosage treatment, the frequency of grade 3 and 4 late diarrhea was significantly greater in male than in female patients (43% [25/58] versus 16% [5/32]; $p=0.01$), but there were no gender differences in the frequency of grade 3 late diarrhea in the other two studies of the weekly dosage treatment schedule. Colonic ulceration, sometimes with gastrointestinal bleeding, has been observed in association with administration of CAMPTOSAR.

Hematology: CAMPTOSAR commonly causes neutropenia, leukopenia (including lymphocytopenia), and anemia. Serious thrombocytopenia is uncommon. When evaluated in the trials of weekly administration, the frequency of grade 3 and 4 neutropenia was significantly higher in patients who received previous pelvic/abdominal irradiation than in those who had not received such irradiation (48% [13/27] versus 24% [67/277]; $p=0.04$). In these same studies, patients with baseline serum bilirubin levels of 1.0 mg/dL or more also had a significantly greater likelihood of experiencing first-cycle grade 3 or 4 neutropenia than those with bilirubin levels less than 1.0 mg/dL (50% [19/38] versus 18% [47/266]; $p<0.001$). There were no significant differences in the frequency of grade 3 and 4 neutropenia by gender. In the clinical studies evaluating the weekly dosage schedule, neutropenic fever (concurrent NCI grade 4 neutropenia and fever of grade 2 or greater) occurred in 3% of the patients; 6% of patients received G-CSF for the treatment of neutropenia. NCI grade 3 or 4 anemia was noted in 7% of the patients receiving weekly treatment; blood transfusions were given to 10% of the patients in these trials.

Body as a Whole: Asthenia, fever, and abdominal pain are generally the most common events of this type.

Cholinergic Symptoms: Patients may have cholinergic symptoms of rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea. If these symptoms occur, they manifest during or shortly after drug infusion. They are thought to be related to the anticholinesterase activity of the irinotecan parent compound and are expected to occur more frequently with higher irinotecan doses.

Hepatic: In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4 liver enzyme abnormalities were observed in fewer than 10% of patients. These events typically occur in patients with known hepatic metastases.

Dermatologic: Alopecia has been reported during treatment with CAMPTOSAR. Rashes have also been reported but did not result in discontinuation of treatment.

Respiratory: Severe pulmonary events are infrequent. In the clinical studies evaluating the weekly dosage schedule, NCI grade 3 or 4 dyspnea was reported in 10% of patients. Over half the patients with dyspnea had lung metastases; the extent to which malignant pulmonary involvement or other preexisting lung disease may have contributed to dyspnea in these patients is unknown.

Neurologic: Insomnia and dizziness can occur, but are not usually considered to be directly related to the administration of CAMPTOSAR. Dizziness may sometimes represent symptomatic evidence of orthostatic hypotension in patients with dehydration.

Cardiovascular: Vasodilation (flushing) may occur during administration of CAMPTOSAR. Bradycardia may also occur, but has not required intervention. These effects have been attributed to the cholinergic syndrome sometimes observed during or shortly after infusion of CAMPTOSAR. Thromboembolic events have been observed in patients receiving CAMPTOSAR; the specific cause of these events has not been determined.

Other Non-U.S. Clinical Trials

Irinotecan has been studied in over 1100 patients in Japan. Patients in these studies had a variety of tumor types, including cancer of the colon or rectum, and were treated with several different doses and schedules. In general, the types of toxicities observed were similar to those seen in U.S. trials with CAMPTOSAR. The information from Japanese trials indicates that patients with considerable ascites or pleural effusions were at increased risk for neutropenia or diarrhea. A potentially threatening pulmonary syndrome, consisting of dyspnea, fever, and a reticulonodular pattern on chest x-ray, was observed in a small percentage of patients in Japanese studies. The contribution of irinotecan to these preliminary events was difficult to assess because these patients also had lung tumors and some had preexisting nonmalignant pulmonary disease. As a result of these observations, however, clinical studies in the United States have enrolled few patients with compromised pulmonary function, significant ascites, or pleural effusions.

Post-Marketing Experience

The following events have been identified during postmarketing use of CAMPTOSAR in clinical practice. Cases of colitis complicated by ulceration, bleeding, and infection have been observed. There have been rare cases of renal impairment and acute renal failure, generally in patients who became infected and/or volume depleted from severe gastrointestinal toxicities (see WARNINGS).

Hypersensitivity reactions including severe anaphylactic or anaphylactoid reactions have also been observed (see WARNINGS).

OVERDOSAGE

In U.S. phase 1 trials, single doses of up to 345 mg/m² of irinotecan were administered to patients with various cancers. Single doses of up to 750 mg/m² of irinotecan have been given in non-U.S. trials. The adverse events in these patients were similar to those reported with the recommended dosage and regimen. There is no antidote for overdosage of CAMPTOSAR. Maximum supportive care should be instituted to prevent dehydration due to diarrhea and to treat any infectious complications.

DOSAGE AND ADMINISTRATION

Combination-Agent Dosage

Dosage Regimens

CAMPTOSAR Injection in Combination with 5-Fluorouracil (5-FU) and Leucovorin (LV)

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes (see Preparation of Infusion Solution). For all regimens, the dose of LV should be administered immediately after CAMPTOSAR, with the administration of 5-FU to occur immediately after receipt of LV. CAMPTOSAR should be used as recommended; the currently recommended regimens are shown in Table 10.

Dosing for patients with bilirubin >2 mg/dL cannot be recommended since such patients were not included in clinical studies. It is recommended that patients be premedicated with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms.

Dose Modifications

Patients should be carefully monitored for toxicity and assessed prior to each treatment. Doses of CAMPTOSAR and 5-FU should be modified as necessary to accommodate individual patient tolerance to treatment. Based on the recommended dose-levels described in Table 10, Combination-Agent Dosage Regimens Modifications, subsequent doses should be adjusted as suggested in Table 11, Recommended Dose Modifications for Combination Schedules. All dose modifications should be based on the worst preceding toxicity. After the first treatment, patients with active diarrhea should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing therapy. Provided intolerable toxicity does not develop, treatment with additional cycles of CAMPTOSAR/5-FU/LV may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 10. Combination-Agent Dosage Regimens & Dose Modifications ^a			
Regimen 1 6-wk cycle with bolus 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU	125 mg/m ² IV over 90 min, d 1,8,15,22 20 mg/m ² IV bolus, d 1,8,15,22 500 mg/m ² IV bolus, d 1,8,15,22	
Starting Dose & Modified Dose Levels (mg/m ²)			
	Starting Dose	Dose Level -1	Dose Level -2
CAMPTOSAR	125	100	75
LV	20	20	20
5-FU	500	400	300
Regimen 2 6-wk cycle with infusional 5-FU/LV (next cycle begins on day 43)	CAMPTOSAR LV 5-FU Bolus 5-FU Infusion ^b	180 mg/m ² IV over 90 min, d 1,15,29 200 mg/m ² IV over 2 h, d 1,2,15,16,29,30 400 mg/m ² IV bolus, d 1,2,15,16,29,30 600 mg/m ² IV over 22 h, d 1,2,15,16,29,30	
Starting Dose & Modified Dose Levels (mg/m ²)			
Starting Dose	Dose Level -1	Dose Level -2	
CAMPTOSAR	180	150	120
LV	200	200	200
5-FU Bolus	400	320	240
5-FU Infusion ^b	600	480	360
^a Dose reductions beyond dose level -2 by decrements of [ap] 20% may be warranted for patients continuing to experience toxicity. Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.			
^b Infusion follows bolus administration.			

Table 11. Recommended Dose Modifications for CAMPTOSAR/5-Fluorouracil (5-FU)/Leucovorin (LV) Combination Schedules		
Patients should return to pre-treatment bowel function without requiring antidiarrhea medications for at least 24 hours before the next chemotherapy administration. A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1500/\text{mm}^3$, and the platelet count has recovered to $\geq 100,000/\text{mm}^3$, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing therapy.		
Toxicity NCI CTC Grade ^a (Value)	During a Cycle of Therapy	At the Start of Subsequent Cycles of Therapy ^b
No toxicity	Maintain dose level	Maintain dose level
Neutropenia		
1 (1500 to 1999/mm ³)	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm ³)	down 1 dose level	Maintain dose level

3 (500 to 999/mm ³)	Omit dose until resolved to \leq grade 2, then down 1 dose level	down 1 dose level
4 ($<500/\text{mm}^3$)	Omit dose until resolved to \leq grade 2, then down 2 dose levels	down 2 dose levels
Neutropenic fever	Omit dose until resolved, then down 2 dose levels	
Other hematologic toxicities	Dose modifications for leukopenia or thrombocytopenia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.	
Diarrhea		
1 (2-3 stools/day $>$ pretx ^c)	Delay dose until resolved to baseline, then give same dose	Maintain dose level
2 (4-6 stools/day $>$ pretx)	Omit dose until resolved to baseline, then down 1 dose level	Maintain dose level
3 (7-9 stools/day $>$ pretx)	Omit dose until resolved to baseline, then down 1 dose level	down 1 dose level
4 (≥ 10 stools/day $>$ pretx)	Omit dose until resolved to baseline, then down 2 dose levels	down 2 dose levels
Other nonhematologic toxicities^d		
1	Maintain dose level	Maintain dose level
2	Omit dose until resolved to \leq grade 1, then down 1 dose level	Maintain dose level
3	Omit dose until resolved to \leq grade 2, then down 1 dose level	down 1 dose level
4	Omit dose until resolved to \leq grade 2, then down 2 dose levels	down 2 dose levels
	<i>For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR</i>	<i>For mucositis/stomatitis decrease only 5-FU, not CAMPTOSAR</i>
^a National Cancer Institute Common Toxicity Criteria (version 1.0)		
^b Relative to the starting dose used in the previous cycle		
^c Pretreatment		
^d Excludes alopecia, anorexia, asthenia		

Single-Agent Dosage Schedules

Dosage Regimens

CAMPTOSAR should be administered as an intravenous infusion over 90 minutes for both the weekly and once-every-3-week dosage schedules (see Preparation of Infusion Solution). Single-agent dosage regimens are shown in Table 12.

A reduction in the starting dose by one dose level of CAMPTOSAR may be considered for patients with any of the following conditions: age ≥ 65 years, prior pelvic/abdominal radiotherapy, performance status of 2, or increased bilirubin levels. Dosing for patients with bilirubin >2 mg/dL cannot be recommended since patients were not included in clinical studies.

It is recommended that patients receive premedication with antiemetic agents. Prophylactic or therapeutic administration of atropine should be considered in patients experiencing cholinergic symptoms. See PRECAUTIONS, General.

Dose Modifications

Patients should be carefully monitored for toxicity and doses of CAMPTOSAR should be modified as necessary to accommodate individual patient tolerance to treatment. Based on recommended dose-levels described in Table 12, Single-Agent Regimens of CAMPTOSAR and Dose Modifications, subsequent doses should be adjusted as suggested in Table 13, Recommended Dose Modifications for Single-Agent Schedules. All dose modifications should be based on the worst pre-treatment toxicity.

A new cycle of therapy should not begin until the toxicity has recovered to NCI grade 1 or less. Treatment may be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicity. If the patient has not recovered, consideration should be given to discontinuing this combination therapy. Provided intolerable toxicity does not develop, treatment with additional cycles of CAMPTOSAR may be continued indefinitely as long as patients continue to experience clinical benefit.

Table 12. Single-Agent Regimens of CAMPTOSAR and Dose Modifications

Weekly

Regimen ^a	125 mg/m ² IV over 90 min, d 1,8,15,22 then 2-wk rest		
	Starting Dose & Modified Dose Levels ^c (mg/m ²)		
	Starting Dose	Dose Level -1	Dose Level -2
	125	100	75
Once-Every-3-Week Regimen ^b	350 mg/m ² IV over 90 min, once every 3 wks ^c		
	Starting Dose & Modified Dose Levels (mg/m ²)		
	Starting Dose	Dose Level -1	Dose Level -2
	350	300	250
^a Subsequent doses may be adjusted as high as 150 mg/m ² or to as low as 50 mg/m ² in 25 to 50 mg/m ² decrements depending upon individual patient tolerance.			
^b Subsequent doses may be adjusted as low as 200 mg/m ² in 50 mg/m ² decrements depending upon individual patient tolerance.			
^c Provided intolerable toxicity does not develop, treatment with additional cycles may be continued indefinitely as long as patients continue to experience clinical benefit.			

Table 13. Recommended Dose Modifications for Single-Agent Schedules ^a

A new cycle of therapy should not begin until the granulocyte count has recovered to $\geq 1500/\text{mm}^3$, and the platelet count has recovered to $\geq 100,000/\text{mm}^3$, and treatment-related diarrhea is fully resolved. Treatment should be delayed 1 to 2 weeks to allow for recovery from treatment-related toxicities. If the patient has not recovered after a 2-week delay, consideration should be given to discontinuing CAMPTOSAR.

Worst Toxicity NCI Grade ^b (Value)	During a Cycle of Therapy	At the Start of the Next Cycles of Therapy (After Adequate Recovery), Compared with the Starting Dose in the Previous Cycle ^a	
	Weekly	Weekly	Once Every 3 Weeks
No toxicity	Maintain dose level	up 25 mg/m ² up to a maximum dose of 150 mg/m ²	Maintain dose level
Neutropenia			
1 (1500 to 1999/mm ³)	Maintain dose level	Maintain dose level	Maintain dose level
2 (1000 to 1499/mm ³)	down 25 mg/m ²	Maintain dose level	Maintain dose level
3 (500 to 999/mm ³)	Omit dose until resolved to <= grade 2, then down 25 mg/m ²	down 25 mg/m ²	down 50 mg/m ²
4 (<500/mm ³)	Omit dose until resolved to <= grade 2, then down 50 mg/m ²	down 50 mg/m ²	down 50 mg/m ²
Neutropenic fever	Omit dose until resolved, then down 50 mg/m ² when resolved	down 50 mg/m ²	down 50 mg/m ²
Other hematologic toxicities	Dose modifications for leukopenia, thrombocytopenia, and anemia during a cycle of therapy and at the start of subsequent cycles of therapy are also based on NCI toxicity criteria and are the same as recommended for neutropenia above.		
Diarrhea			
1 (2-3 stools/day > pretx ^c)	Maintain dose level	Maintain dose level	Maintain dose level
2 (4-6 stools/day > pretx)	down 25 mg/m ²	Maintain dose level	Maintain dose level
3 (7-9 stools/day > pretx)	Omit dose until resolved to <= grade 2, then down 25 mg/m ²	down 25 mg/m ²	down 50 mg/m ²
4 (>= 10 stools/day > pretx)	Omit dose until resolved to <= grade 2, then down 50 mg/m ²	down 50 mg/m ²	down 50 mg/m ²
Other nonhematologic toxicities ^d			
1	Maintain dose level	Maintain dose level	Maintain dose level
2	down 25 mg/m ²	down 25 mg/m ²	down 50 mg/m ²
3	Omit dose until resolved to <= grade 2, then down	down 25 mg/m ²	down 50 mg/m ²

	25 mg/m ²		
4	Omit dose until resolved to \leq grade 2, then down 50 mg/m ²	down 50 mg/m ²	down 50 mg/m ²
^a All dose modifications should be based on the worst preceding toxicity			
^b National Cancer Institute Common Toxicity Criteria (version 1.0)			
^c Pretreatment			
^d Excludes alopecia, anorexia, asthenia			

Preparation & Administration Precautions

As with other potentially toxic anticancer agents, care should be exercised in the handling and preparation of infusion solutions prepared from CAMPTOSAR. The use of gloves is recommended. If a solution of CAMPTOSAR contacts the skin, wash the skin immediately and thoroughly with soap and water. If CAMPTOSAR contacts the mucous membranes, flush thoroughly with water. Several published guidelines for handling and disposal of anticancer agents are available.¹⁻⁷

Preparation of Infusion Solution

Inspect vial contents for particulate matter and repeat inspection when drug product is withdrawn from vial into syringe.

CAMPTOSAR Injection must be diluted prior to infusion. CAMPTOSAR should be diluted in 5% Dextrose Injection, USP, (preferred) or 0.9% Sodium Chloride Injection, USP, to a final concentration range of 0.12 to 2.8 mg/mL. In most clinical trials, CAMPTOSAR was administered in 250 mL to 500 mL of 5% Dextrose Injection.

The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in 5% Dextrose Injection, USP, and stored at refrigerated temperatures (approximately 2° to 8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using 0.9% Sodium Chloride Injection, USP, is not recommended due to a low and sporadic incidence of visible particulates. Freezing CAMPTOSAR and admixtures of CAMPTOSAR may result in precipitation of the drug and should be avoided. Because of possible microbial contamination during dilution, it is advisable to use the admixture prepared with 5% Dextrose Injection, USP, within 24 hours if refrigerated (2° to 8°C, 36° to 46°F). In the case of admixtures prepared with 5% Dextrose Injection, USP, or Sodium Chloride Injection, USP, the solutions should be used within 6 hours if kept at room temperature (20° to 25°C, 68° to 77°F).

Other drugs should not be added to the infusion solution. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

HOW SUPPLIED

Each mL of CAMPTOSAR Injection contains 20 mg irinotecan (on the basis of the trihydrate salt); 45 mg sorbitol; and 0.9 mg lactic acid. When necessary, pH is adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid.

CAMPTOSAR Injection is available in single-dose amber glass vials in the following package sizes:

2 mL..... NDC 0009-7529-02

5 mL..... NDC 0009-7529-01

This is packaged in a backing/plastic blister to protect against inadvertent breakage and leakage. The vial should be inspected for damage and visible signs of leakage before removing the backing/plastic blister. If damaged, incinerate the unopened package.

Store at controlled room temperature 15° to 30°C (59° to 86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in carton until the time of use.

Rx only

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